LISTING OF CLAIMS

This listing of claims will replace all prior versions, and listing, of claims in the application:

Listing of Claims:

Claims 1. – 93. (Canceled)

Claim 94. (Previously Presented) A method for quantitative structure function analysis research on biologically active proteins or peptides having a receptor binding center and a catalytic binding center, said method comprising applying a specific chemical modification of selected amino acids specifically directed to said catalytic activity center of said proteins or said peptides without distortion of said receptor binding center whereby said modification results in said proteins and said peptides having at least one feature selected from the group consisting of enhanced biological activity, enhanced stability, suppressed antigenicity, acquired antagonistic activity, and cell inhibitory activity and at the same time without distortion of receptor binding activity of said receptor binding, said method comprising:

a) gradual chemical modification of a protein or peptide, followed by

b) monitoring the modification reaction with a mild and sensitive method comprising nondenaturing electrophoresis or electrospray mass spectrometry and optionally confirming the overall structural integrity;

c) protease treatment;

d) mass spectrometry; and/or

e) assaying biological activity of the modified product and optionally assaying stability of the modified protein.

Claim 95. (Previously Presented) The method according to claim 94, wherein said proteins or peptides are selected from the group consisting of interleukins, haemopoietic growth factors, peptide hormones, protein hormones, signal peptides and signal proteins.

Claim 96. (Previously Presented) The method according to claim 94, wherein said protein or peptide is selected from the group consisting of cytokine superfamily, insulin, and prolactin.

Claim 97. (Previously Presented) The method according to claim 96, wherein said protein or peptide is a member of the cytokine superfamily selected from the group consisting of interleukins 1-8, interleukin 10, CM-CSF, TNF, gamma IFN and EPO.

Claim 98. (Previously Presented) The method according to claim 97, wherein said protein or peptide is an interleukin selected from interleukins 1-7.

Claim 99. (Previously Presented) The method according to claim 94, wherein specific digestion with specific proteases and mass spectrometry is carried out for characterisation and localisation of the modified amino acids.

Claim 100. (Previously Presented) The method according to claim 94 or 99, wherein specific digestion with specific endoproteases and laser desorption mass spectometry is carried out for characterization and localization of the modified amino acids.

Claim 101. (Previously Presented) The method according to claim 100, wherein said endoprotease is Endo Glu C or Endo Lys C.

Claim 102. (Previously Presented) The method according to claim 94 or 99, wherein the modification is carried out by specific digestion with specific exoproteases and

electrospray mass spectrometry is carried out for characterisation and localisation of the modified amino acids.

Claim 103. (Previously Presented) The method of claim 102, wherein the exoprotease is Cathepsine C or carboxypeptidase Y.

Claim 104. (Previously Presented) The method according to claim 94 or 99, wherein said chemical modification comprises alkylation or acylation, said chemical modification being conducted while gradually varying at least one of the conditions under which said modification is conducted, said conditions comprising a pH in a range between a pH of 5.0 and 7.0, the time for conducting said modification, and reagent concentrations.

Claim 105. (Previously Presented) The method according to claim 104, wherein the modification is carried out in the presence of phosphate buffer and, optionally in combination with acetic anhydride.

Claim 106. (Previously Presented) The method according to claim 94 or 99, for the introduction of an antagonistic or cell inhibitory activity, wherein the modification has specificity to one or more residues that are involved in catalytic activity.

Claim 107. (Previously Presented) The method according to claim 94 or 99, wherein the modification is within or in close proximity to a Zinc binding center, and said residue is a histidine residue.

Claim 108. (Previously Presented) The method according to claim 94 or 99, wherein the modification further comprises reversibly denaturing the peptides or proteins and adding chelating agent to remove the metal ion.

Claim 109. (Previously Presented) The method according to claim 94 or 99, wherein the modification is specific for one type of amino acid, specific to one amino acid, or is specific for only one amine-residue in the peptide or protein.

Claim 110. (Previously Presented) A method for quantitative structure function analysis research on a biologically active protein or peptide that comprises human interleukin 3 having a receptor binding center and a catalytic binding center, said method comprising applying a specific chemical modification of selected amino acids specifically directed to said catalytic activity center of said human interleukin 3 without distortion of the receptor binding center whereby said modification results in a modified human interleukin 3 having at least one feature selected from the group consisting of enhanced biological activity, enhanced stability, suppressed antigenicity, acquired antagonistic activity, and cell inhibitory activity, and at the same time without distortion of receptor binding activity of said receptor binding center, wherein the human interleukin 3 is modified only at one or more of the following residues: Ala^{1}, His^{26}, Lys^{28}, Lys^{66}, His^{95}, His^{98}, Lys^{100}, or Lys^{116}, said method comprising:

a) gradual chemical modification of human interleukin 3, followed by

b) monitoring the modification reaction by nondenaturing electrophoresis or electrospray mass spectrometry and optionally confirming the overall structural integrity;

c) localizing and characterizing the modified residues in said modified human interleukin 3 by digesting said modified human interleukin with a protease, and analyzing said human interleukin 3 and said modified human interleukin with mass spectrometry; and

d) assaying the biological activity of the modified human interleukin 3 and optionally assaying stability of the modified human interleukin 3.

Claim 111. (Previously Presented) The method according to claim 94 or 99, for the introduction of an antagonistic and/or cell inhibitory activity, said method comprising disruption of phosphate binding.

Claims 112. – 132. (Canceled)

Claim 133. (Previously Presented) The method according to claim 94 or 99, wherein said chemical modification comprises alkylation using iodo acetate, or acetylation using acetic anyhydride or using succinic anhydride, said chemical modification being conducted while gradually varying at least one of the conditions under which said chemical modification is conducted, said conditions comprising a pH range between a pH of 5.0 and 7.0, time for conducting said modification, and reagent concentrations.

Claim 134. (Canceled)

Claim 135. (Canceled)

Claim 136. (Previously Presented) The method according to claim 108, wherein the chelating is conducted in the presence of urea and EDTA.

Claim 137. (Previously Presented) The method according to claim 94, wherein the modified protein or modified peptide is a modified signal substance selected from the group consisting of a protein hormone, peptide hormone, growth factor, a haemopoeitic growth factor, an inteferon, an interleukin and a colony stimulating factor with enhanced biological activity, antagonistic activity or cell inhibitory activity, wherein said signal substance contains a modification within or in such close proximity to a catalytic center that it effects a biological or chemical feature.

Claim 138. (Previously Presented) The method according to claim 94, wherein said modified substance is modified interleukin 3.

Claim 139. (Previously Presented) The method according to claim 110, wherein said modified substance comprises at least one of

a) 0.1 ng of the substance, modified IL-3 inhibits up to approximately 50% of 3 ng/ml native IL-3;

b) 3 ng/ml of the substance, modified IL-3 suppresses 80-90% thymidine incorporation of 30-100 ng/ml control IL-3; or

c) the substance modified IL-3 inhibits control IL-3 by a factor of 10-100.

Claim 140. (Previously Presented) The method according to claim 94, wherein the modified protein or modified peptide obtained has acquired one of the following combinations of characteristics:

a) a decreased stability and increased antagonistic activity;

b) a decreased stability and increased agonistic activity;

c) an increased stability and antagonistic activity; or

d) an increased stability in combination with an agonistic activity.

Claim 141. (Previously Presented) The method according to claim 110, wherein the modified protein or modified peptide is

a) acetylated IL-3;

b) an N-terminally proteased IL-3;

c) succinylated IL-3; or

d) a C-terminally proteased IL-3.

Claim 142. (Canceled)